

The pending claims are directed to a combination therapy invention (method and related pharmaceutical composition) described by the pending application. Support for these claims in the pending application (and in the original provisional application Serial No. 60/044,626) was detailed in a previous response (see Amendment A).

At a previous interview with Examiners Jagoe and Rose, the patentability of claims 13-39 submitted with Amendment A was discussed. Based on the interview, amended claims directed specifically to methods and compositions wherein the COX-2 inhibitor, or its pharmaceutically acceptable salt, is used in combination with a lipid lowering drug were presented in Amendment B. Use of the COX-2 inhibitor and a statin is specifically claimed.

The Office communication states that the rejection of Claims 1-39 as being unpatentable, under 35 USC 103(a), over Searle WO 95/15316 in view of the Merck Manual needs to be addressed in order for the previous response to be fully responsive. As noted in Amendment B, the cancellation of claims 1-12 makes it unnecessary to reply to that aspect of this rejection. As regards pending claims 13, 15-24, 26-32 and 34-39, this rejection is respectfully traversed.

In the prior response, applicants argued (as their undersigned representative previously urged without objection from the Examiner's at the interview) the prior issuance of U.S. 6,245,797 underscored the patentability of the subject matter embraced by applicants' pending amended claims, since that same subject matter had already been considered to be patentable by the USPTO (in the issued '797 patent) and thus must be patentable over the cited combination of documents. The same combination of documents cited in the present Office Action would be prior art to the '797 patent. Indeed, the possible need for instituting an interference between the '797 patent and the pending application was specifically discussed during the previous interview.

The similarities of the claimed subject matter to the invention claimed in the '797 patent is unmistakable. As described in prior Amendment A, U.S. 6,245,797, *inter alia*, claims a method for reducing the risk of developing atherosclerotic disease by using a combination of an HMG-CoA reductase inhibitor and a COX-2 inhibitor. It is our understanding that HMG-CoA reductase inhibitors are also known as statins. By virtue

of the April 18, 1997 filing date of applicants' provisional application, the '797 patent is not citable against the subject application as prior art under §§102 and 103 of the Patent Statute. As especially shown by a comparison of pending claim 24 and issued claim 1 of the '797 patent, the two inventions are substantially indistinguishable.

On the basis of the prior issuance of the '797 patent, applicants again assert that the pending claims should be found patentable over the cited combination of documents. In addition and as explained in more detail below, the claims also should be found patentable because the cited combination simply does not present a valid *prima facie* case for obviousness.

The prior Office Action acknowledges that the "claims are drawn to prophylactic treatment of a subject at risk of developing a cardiovascular disorder comprising treating a subject with a COX-2 inhibitor and *inter alia* a lipid lowering drug as a statin." The Office Action asserts that the WO publication teaches that "COX-2 inhibitors would be useful for conditions such as vascular disease and myocardia ischemia and the like (page 7, lines 8-36)." The Office Action further asserts that the cited Merck Manual "teaches that HMG-CoA reductase inhibitors (statins) can lower LDL levels and prevent unstable angina and MI and decrease the need for surgical coronary revascularization."

The Office Action then argues that "[i]t is *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose" implying implicitly that the invention defined by the pending claims is nothing but such an obvious combination. However, the cited documents do NOT teach that the separate compositions recited in the pending claims are useful "for the very same purpose." The Office Action jumps to this conclusion without any critical analysis of the actual teachings of the cited documents. Furthermore, neither of the cited documents provides a valid basis for its combination with the other. The combination posed by the Office Action has resulted from an improper hindsight evaluation of the invention defined by the pending claims. For these reasons, the rejection based on Section 103 must be withdrawn.

WO 95/15316 teaches that the recited compounds, a particular class of selective COX-2 inhibitors, are useful for the treatment of **inflammation** (page 7, lines 8-10). The

cited WO publication specifically teaches that “[c]ompounds of Formula I would be useful in **treating inflammation** in such diseases as vascular diseases ... myocardial ischemia and the like” (page 10, lines 27-36). It was on the basis of this disclosure that the Office Action apparently asserted, as reported above, that the WO publication teaches that “COX-2 inhibitors would be useful for conditions such as vascular disease and myocardia ischemia and the like (page 7, lines 8-36).” This assertion in the Office Action, however, is an improper and incorrect over-generalization of the actual teachings of the document. As noted, the document merely teaches that such compounds are useful for treating **inflammation** associated with such conditions – not that the compounds are useful for treating the condition itself. The jump from the treatment of inflammation to the treatment of the disease itself is simply unsupported by any valid interpretation of the WO publication.

Since, properly interpreted, the WO publication does not remotely suggest that the illustrated compounds can be used to treat either vascular disease, or myocardia ischemia, the WO document also provides absolutely no motivation for using such compounds for prophylactically treating a subject at risk of developing a cardiovascular disorder. Surely, there is no evidence in the present record that a subject at risk of developing a cardiovascular disorder needs to be treated for inflammation.

The only independent claims of the pending application, claims 13, 24 and 32, are specifically directed to the “prophylactic treatment of a subject at risk of developing a cardiovascular disorder,” to the prevention of “atherosclerosis in a subject at risk of developing atherosclerosis and to a pharmaceutical composition, respectively, each characterized by requiring a combination of a COX-2 inhibitor and a “lipid-lowering drug.” The cited WO publication simply contains NO teaching that would make it obvious to use a COX-2 anti-inflammatory drug in such instance, let alone in combination with the required “lipid-lowering drug.”

The citation to the Merck Manual does not remedy any of the shortcomings of the cited primary reference.

The Merck Manual is cited for its purported teaching “that HMG-CoA reductase inhibitors (statins) can lower LDL levels and prevent unstable angina and MI and decrease the need for surgical coronary revascularization.” This teaching, however,

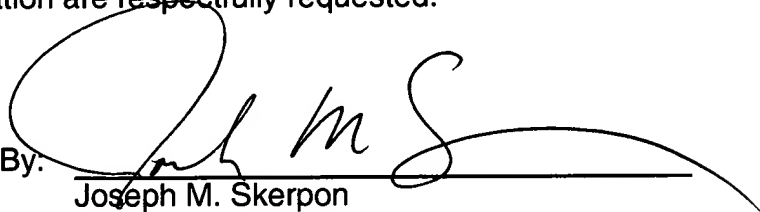
does NOT provide any basis on which the cited combination can be justified. There is simply no connection between the anti-inflammatory activity of the recited compounds of the WO publication and the LDL lowering activity of the statins described in the Merck Manual. In the absence of such a nexus, there is simply no motivation for using a combination of an anti-inflammatory and a lipid-lowering drug.

The Office Action has selected these references purely from a hindsight consideration of applicants' pending claims. This is improper. The Office Action's only justification for selecting these disparate disclosures for consideration in combination was that they each teach compositions to be useful for the same purpose. That justification is purely and simply incorrect. The compositions of the respective documents are NOT taught to be useful for the same purpose. It is black letter law that a combination constructed from hindsight does not present a prima facie case of obviousness.

Consequently, based on the above, prompt reconsideration and full allowance of the claims pending in the subject application are respectfully requested.

Date: May 17, 2002

By:

A handwritten signature in black ink, appearing to read 'JMS', is written over a horizontal line.

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